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Formal Asymmetric Hydration of Non-Activated Alkenes in Aqueous Medium through a "Chemoenzymatic Catalytic System"

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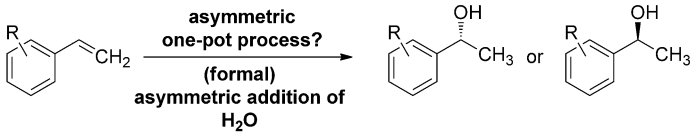
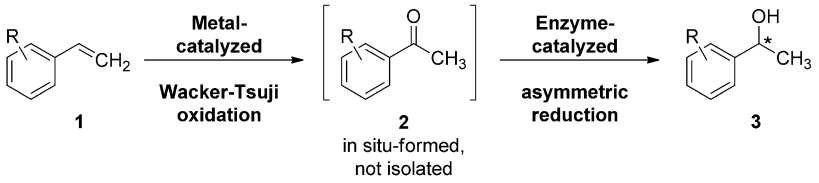
Today on both laboratory and industrial scale a very prominent strategy for the enantioselective synthesis of secondary aromatic alcohols is based on a transformation of (a substituted) benzene into (a substituted) acetophenone, for example, by using Friedel–Crafts-type chemistry, and subsequent enantioselective reduction.[1] In contrast, the highly attractive alternative of a direct asymmetric transformation of non-activated alkenes, such as styrene, into the corresponding secondary alcohols still represents a "dream reaction" for organic chemists.[2,3,4] The reaction concept of such a formal hydration process is shown in Scheme 1.



Scheme 1. Challenge of a (formal) asymmetric hydration process.

So far to the best of our knowledge a reliable, broadly applicable and efficient chiral catalyst suitable for such a direct transformation has not been found.[2,3] In the following we report a "chemoenzymatic catalytic system" (instead of a single catalyst molecule), which enables exactly this desired direct one-pot transformation of (substituted) styrene(s) into the corresponding (substituted) phenylethan-1-ol(s) in a highly enantioselective fashion, thus fulfilling the prerequisites for the challenging process described above and in Scheme 1. The key feature of this "catalytic system", which works in an aqueous reaction medium, is the combination of a palladium component and an enzyme component. This formal hydration process is based on a chemoenzymatic one-pot, two-step process in water comprising a Wacker–Tsuji oxidation and subsequent enantioselective reduction of the in situ-formed (substituted) acetophenone under formation of (the substituted) phenylethan-1-ol (Scheme 2). Thus, this process formally corresponds to the unknown reaction type of an asymmetric hydration of a non-activated alkene.

The first focus was on the development of a Wacker-type oxidation[5] in aqueous reaction medium, which would enable a subsequent combination with an in situ enantioselective reduction process. After screening a range of Wacker-type oxidations of styrene and analyzing carefully the side- and trace-product spectra as well as the biocompatibility with the metal catalyst components, we found a



Scheme 2. One-pot process corresponding to a formal hydration.

method developed by Tsuji as most suitable for our purpose.[6] When using the original reaction conditions[6] such as $PdCl_2$ as a palladium catalyst, benzoquinone as oxidation reagent, and DMF/water (7:1 (v/v)), however, a low conversion of only 34% and 80% selectivity for acetophenone was observed. Subsequently, we conducted a solvent optimization (for details, see Supporting Information) and we were pleased to find that when using a mixture of methanol and water (7:1 (v/v)) the desired acetophenone (**2a**) was formed with >99% conversion and 90% selectivity (Scheme 3, route A, [Eq. (1)]). As side products *O*-methylphenylethan-1-ol (3%), phenylacetaldehyde dimethyl acetal (2%), methyl phenylacetate (3%), and traces of racemic phenylethan-1-ol (1%) are formed. Notably, this process runs at a high substrate concentration of 1.3 M of styrene (**1a**). The subsequent reduction of acetophenone to the corresponding

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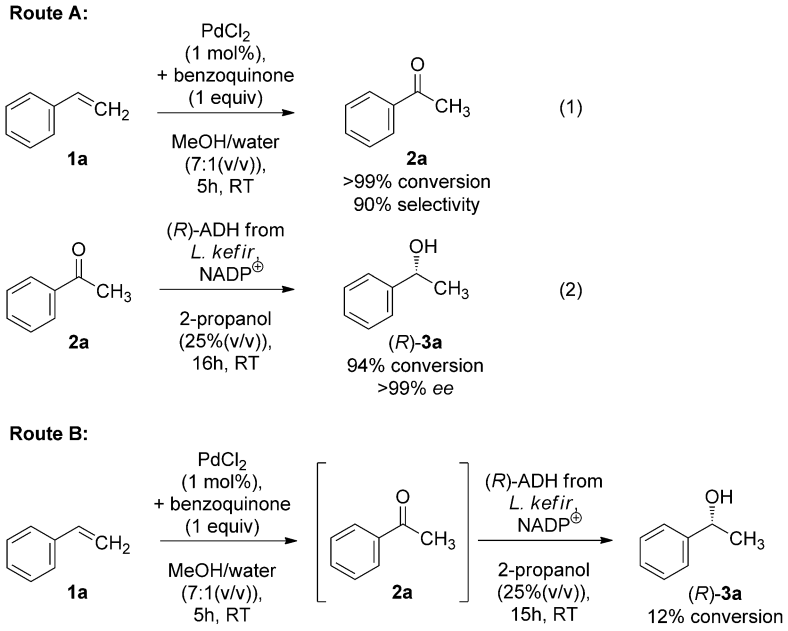
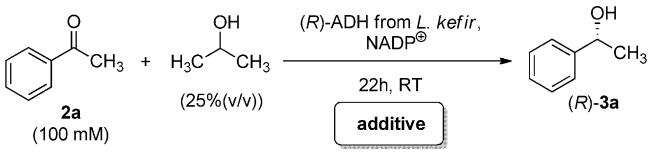


Scheme 3. Sequential synthesis of (*R*)-**3a** (route A) versus one-pot process (route B).

enantiomerically enriched secondary alcohol can be done by either chemocatalytic or enzymatic methods.[1,7] When starting from pure acetophenone (**2a**) and using an alcohol dehydrogenase from *Lactobacillus kefir* as an enzyme component in combination with 2-propanol (25% (v/v)) as reducing reagent, we obtained the desired (*R*)-phenylethan-1-ol, (*R*)-**3a**, with 94% conversion and >99% *ee* (Scheme 3, route A, [Eq. (2)]).

Next, we combined these two separate steps, which run efficiently with high conversions when conducted in a separated mode, into a one-pot process. In our initial attempt, however, such a one-pot process, which formally corresponds to the desired hydration process, only resulted in a non-satisfactory, low conversion of 12% for the reduction step (Scheme 3, route B). It became clearly evident that at least one component in the reaction mixture of the Wacker–Tsuji oxidation has a strong negative impact on the biotransformation. Since we initially assumed the palladium component $Pd^{II}Cl_2$ or an aqueous Pd^{II} derivative thereof to be responsible for this negative effect we conducted the biotransformation in the presence of such components as an additive and compared the results with the biotransformations in the absence of such additives (Table 1, entries 1 and 2 versus 3 and 4). Since there was an unchanged high conversion of 91% and 94%, respectively, in the absence and presence of the palladium salts $Pd^{II}Cl_2$ and $K_2Pd^{II}Cl_4$ (Table 1, entries 3 and 4), components other than these palladium complexes have to be the reason for the observed strong negative impact on the enzyme. An even more surprising result was that also the oxidation reagent benzoquinone and by-product hydroquinone as further components being present in the Wacker–Tsuji oxidation did not influence the biotransformation significantly, leading to the desired product (*R*)-**3a** with 90% and 91% conversion, respectively (Table 1, entries 5 and 6). A further explanation could be that one or more side products resulting from the Wacker–Tsuji oxidation (which proceeds with a high conversion but incomplete selectivity of 90%) inhibit or deactivate the enzyme. Accordingly, we studied the impact of the organic crude product resulting from the Wacker–Tsuji oxidation as an "additive", but once again a high conversion of 91% remained for the biotransformation (Table 1, entry 7). Surprisingly, however, when using the aqueous phase resulting from the work-up of the Wacker–Tsuji oxidation reaction as an "additive" in the biotransformation, a strong drop in conversion to 14% was observed (Table 1, entry 8), thus being in the same range as the low conversion in the initial one-pot process (12%, Scheme 3, route B).

Table 1. Impact of additives on the biotransformation.

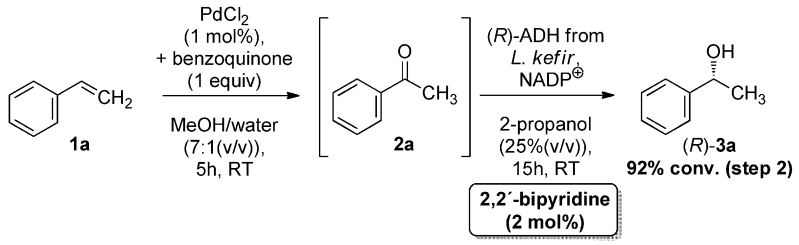


Entry	Additive	Conv. [%]	*ee* [%]
1	none	91	>99
2	none[a]	94	n.d.[b]
3	$PdCl_2$ (1 mM)	91	>99
4	$K_2[PdCl_4]$ (0.5 mM)[a]	94	n.d.[b]
5	hydroquinone (100 mM)	90	>99
6	benzoquinone (10 mM)	91	>99
7	organic crude product (from step 1)	91	n.d.[b]
8	aqueous phase (from step 1)[a]	14	n.d.[b]

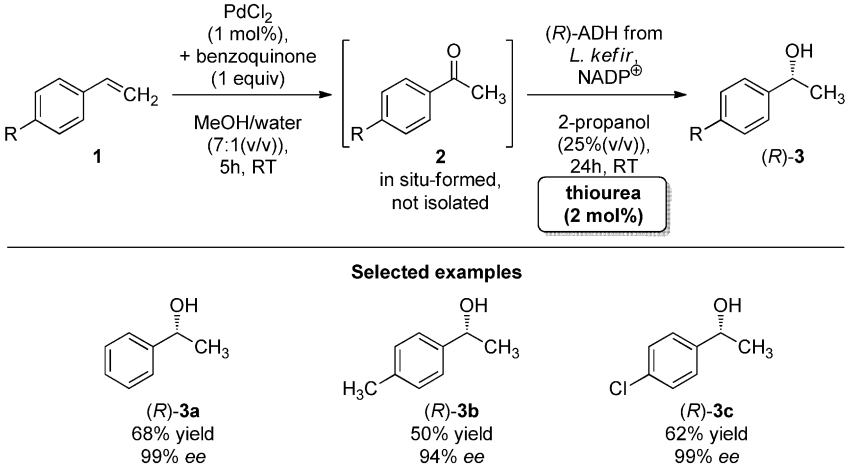
[a] In these reactions, a substrate concentration of 50 mM of acetophenone (**2a**) was used. [b] n.d. = not determined.

Accordingly, suppression of the enzyme-inhibiting or enzyme-deactivating component(s) in the aqueous phase which causes the drop in conversion of the biotransformation is the key prerequisite for developing the desired one-pot process. Since we expected a palladium species, which is formed in the Wacker–Tsuji oxidation, to be present in the aqueous phase and to play a key role in negatively influencing the biotransformation, we screened several organic mol-

ecules as additives in catalytic amounts, which are known to complex Pd^{II} components.[8] We were pleased to find that when adding only 2 mol% of 2,2'-bipyridine as an enzyme-compatible and metal-inhibiting ligand of a palladium species, we succeeded in realizing the desired one-pot process, which corresponds to a "formal" asymmetric hydration process. Starting from styrene (**1a**), and in the presence of a "chemoenzymatic catalytic system", consisting of a palladium-type catalyst and an alcohol dehydrogenase, the desired phenylethan-1-ol (*R*)-**3a** was formed in the one-pot synthesis with excellent conversion of 92% (for the biotransformation; Scheme 4). Thus, the overall conversion is now in the range expected from the conversions obtained in the individual reaction steps carried out in a separated fashion, indicating that by means of the additive ("inhibiting ligand") the reaction mixture of the Wacker–Tsuji oxidation is (bio)compatible with the subsequent enzymatic reduction process. Besides 2,2'-bipyridine, other organic molecules turned out to be highly suitable for this process, such as thiourea and EDTA, which led to conversions of 93% and 92%, respectively, when being used in a catalytic amount of 2 mol% (see the Supporting Information for details).



Scheme 4. Optimized chemoenzymatic one-pot process in water.



Scheme 5. Substrate scope of the one-pot process.

Furthermore, an initial study on the substrate scope of this new one-pot synthesis and formal asymmetric hydration process has been carried out using thiourea (2 mol%) as an economically very attractive additive (Scheme 5). In addition to styrene, which was transformed into (*R*)-phenylethan-1-ol in 68% yield and with an excellent enantiomeric excess of 99% *ee*, substituted styrene derivatives also turned out to be suitable substrates. When starting from *p*-methylated styrene (**1b**), the resulting alcohol (*R*)-**3b** was obtained in 50% yield and with 94% *ee*, whereas the use of *p*-chlorostyrene (**1c**), as a substrate led to the desired product (*R*)-**3c** in 62% yield and with 99% *ee* (Scheme 5).

In conclusion, a one-pot synthesis has been developed that enables the direct one-pot conversion of (substituted) styrene(s) of type **1** into (substituted) (*R*)-phenylethan-1-ol(s), (*R*)-**3**, in a highly enantioselective manner. Such an enantioselective synthesis of a secondary alcohol corresponds formally to the reaction type of an asymmetric hydration of a non-activated alkene. The key feature of this efficient one-pot process is the use of a "chemoenzymatic catalytic system", consisting of an enzyme-compatible palladium species and an enzyme, instead of a single catalyst molecule. This "chemoenzymatic catalytic system" enables a one-pot, two-step process in water comprising a palladium-catalyzed Wacker–Tsuji oxidation and subsequent enantioselective enzymatic reduction of the in situ-formed (substituted) acetophenone(s) of type **2** under formation of (substituted) (*R*)-phenylethan-1-ol(s), (*R*)-**3**. Thus, this process is a further example of the power of chemoenzymatic one-pot syntheses in water for challenging asymmetric transformations. In future work, the expansion of the substrate scope of this process technology, further process development, the mechanistic clarification of the additive effect, and scale up are planned.[9]

Acknowledgements

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Keywords: alcohols · asymmetric hydration · enzyme catalysis · palladium · synthetic methods

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[9] As part of the expansion of the substrate scope of this process technology, enantioselective synthesis of further (*R*)-alcohols as well as the development of an analogous synthetic access to the corresponding (*S*)-alcohols are planned.

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